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Adrenal incidentaloma in adults — management recommendations by the Polish Society of Endocrinology

Przypadkowo wykryty guz nadnercza (incydentaloma) u dorosłych — zasady postępowania rekomendowane przez Polskie Towarzystwo Endokrynologiczne

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Abstract

Introduction: A wide use of imaging techniques results in more frequent diagnosis of adrenal incidenataloma.
Aim: To analyse the current state of knowledge on adrenal incidentaloma in adults in order to prepare practical management recommendations.
Methods: Following a discussion, the Polish Society of Endocrinology expert working group have analysed the available data and summarised the analysis results in the form of recommendations.
Imaging and hormonal assessment: Unenhanced adrenal computed tomography (CT) may be recommended as an initial assessment examination helpful in the differentiation between adenomas and "non-adenomatous" lesions. In the case of density > 10 Hounsfield units, CT with contrast medium washout assessment or MRI are recommended. However, in all patients with adrenal incidentaloma, hormonal assessment is recommended in order to exclude pheochromocytoma and hypercortisolism, notwithstanding the clinical picture or concomitant diseases. In addition, examination to exclude primary hyperaldosteronism is suggested in patients with diagnosed hypertension or hypokalaemia.
Treatment: Surgical treatment should be recommended in patients with adrenal incidentaloma, where imaging examinations suggest a malignant lesion (oncological indication) or with confirmed hormonal activity (endocrinological indication). The basis of the surgical treatment is laparoscopic adrenalectomy. Patients with suspected pheochromocytoma must be pharmacologically prepared prior to surgery. In patients not qualified for surgery, control examinations (imaging and laboratory tests) should be established individually, taking into consideration such features as the size, image, and growth dynamics of the tumour, clinical symptoms, hormonal tests results, and concomitant diseases. **(Endokrynol Pol 2016; 67 (2): 234–258)**

Key words: *adrenal incidentaloma; adrenocortical carcinoma; pheochromocytoma; Cushing syndrome; hypercortisolism; management guidelines*

Streszczenie

Wstęp: Szerokie zastosowanie badań obrazowych klatki piersiowej i jamy brzusznej skutkuje coraz częstszym przypadkowym rozpoznawaniem zmian w nadnerczach.
Cel: Celem pracy była analiza dostępnej wiedzy dotyczącej postępowania w incydentaloma nadnerczy u dorosłych w celu przygotowania praktycznych zaleceń.
Sposób przygotowania: Grupa robocza stworzona z ekspertów zgromadzonych w Polskim Towarzystwie Endokrynologicznym przeanalizowała jakość dostępnych danych i po dyskusji podsumowała wyniki analizy w postaci przygotowanych zaleceń.
Ocena obrazowa i hormonalna: Jednofazowa tomografia komputerowa (CT) nadnerczy może być zalecana jako badanie w początkowej ocenie zmiany pozwalające odróżnić gruczolaki od innych zmian nie będących gruczolakami („nie-gruczolaki"). W przypadku gęstości zmiany > 10 jednostek Hounsfielda zaleca się wykonanie badania CT z oceną wypłukiwania środka cieniującego lub rezonansu magne-

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tycznego. U wszystkich chorych z incydentaloma nadnerczy, niezależnie od obrazu klinicznego oraz chorób współistniejących, zaleca się ocenę hormonalną w kierunku guza chromochłonnego oraz hiperkortyzolemii. Badania w kierunku pierwotnego hiperaldosteronizmu są wskazane u pacjentów z rozpoznanym nadciśnieniem tętniczym lub hipokaliemią.
Leczenie: Leczenie operacyjne powinno być zastosowane u chorych z incydentaloma nadnercza o charakterystyce obrazowej mogącej odpowiadać nowotworom złośliwym (wskazania onkologiczne) lub potwierdzonej czynności hormonalnej (wskazania endokrynologiczne). Podstawową metodą leczenia operacyjnego jest laparoskopowa adrenalektomia. Pacjenci z podejrzeniem guza chromochłonnego bezwzględnie wymagają przygotowania farmakologicznego do operacji. U chorych niezakwalifikowanych do operacji, badania kontrolne (obrazowe i laboratoryjne), należy ustalać indywidualnie, biorąc pod uwagę, między innymi wielkość, obraz i dynamikę wzrostu guza, objawy kliniczne, wyniki badań hormonalnych oraz choroby współistniejące. **(Endokrynol Pol 2016; 67 (2): 234–258)**

Słowa kluczowe: *incydentaloma nadnercza; rak kory nadnerczy; pheochromocytoma; zespół Cushinga; hiperkortyzolemia; zalecenia postępowania*

I. The basic goals in the diagnosis and treatment of adrenal incidentaloma

An adrenal incidentaloma is a previously unsuspected adrenal mass with a diameter ≥ 1 cm discovered on chest or abdomen imaging examination [1–4]. Every suspicion of an adrenal lesion observed during ultrasound (US) must be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). There are no reliable or absolute standards concerning adrenal thickness, although it is safe to assume that adrenal thickness in the transverse axis > 1 cm is abnormal. Nevertheless, the thickness of the normal adrenal, especially in the adrenal branches conjunction, may be larger; therefore, confirmation of lesions < 1 cm may be difficult.

Wide use of imaging techniques results in more frequent diagnosis of adrenal lesions, which affects 4% of middle-aged patients and increases to over 10% in the elderly.

Adrenal lesions can be classified as benign or malignant, they may be hormonally active or inactive, as well as unilateral or bilateral (Table I). However, the majority of cases (about 80%) are constituted by benign adenomas or nodular adrenocortical hyperplasia. The incidence of adrenocortical carcinoma (ACC) is estimated at about 5%, pheochromocytoma constitutes about 5%, and metastases about 2% (*please refer to the subdivision concerning histopathological examination*).

For diagnostic and therapeutic purposes, in patients with incidentaloma, two major goals should be set forward:

— **The diagnosis of all ACC cases**. ACC is a rare malignant carcinoma, with a strong tendency for local invasion and distant metastases. The prognosis in ACC is poor (five-year survival <50%), with limited therapeutic options [5–6]. Thus, early diagnosis and radical surgical treatment are crucial.
— **The diagnosis of all hormonally active tumours**. Failure to diagnose tumours secreting catecholamine, cortisol, and aldosterone may lead to life threatening or chronic complications.

In order to achieve the aforementioned goals, it is necessary to analyse both the clinical picture and additional examination results based on laboratory tests and imaging [7–9].

II. Which imaging examinations should be performed in adrenal incidentaloma patients?

The main goal of imaging examinations is the differentiation between adenomas and "non-adenomas" which require further diagnostic steps for ACC, adrenal metastases, or pheochromocytoma. The basic imaging examinations include [10–12]:

1. Unenhanced adrenal CT

— First-line imaging examination in adrenal tumour diagnostics may be unenhanced high-resolution CT (layers < 3 mm). Its advantage is low price, short duration, and no necessity to use a contrast medium. However, in some cases it is necessary to perform further imaging examinations.
— On the basis of an unenhanced CT it is possible to asses such tumour features as the size (additionally, in further tests it is possible to assess its growth dynamics), shape, radiation attenuation coefficient (in Hounsfield units [HU]), and structure homogeneity (including calcifications, necrotic areas).
— The basic examination interpretation: values smaller or equal to +10 HU represent a high lipid content and are typical for adenomas (sensitivity 71%, specificity 98%). In such cases, further imaging tests are usually not necessary. If the values exceed 30 HU it may suggest a pheochromocytoma or a malignant tumour (ACC or adrenal metastases). In contrast, lesions with a radiation attenuation coefficient between 11 and 30 HU are ambiguous; thus, in the differential diagnosis lipid-poor adenomas must be taken into account. Furthermore, lesions with a radiation attenuation coefficient < –20HU are characteristic for myelolipomas.

Table I. *Adrenal incidentaloma in adults*

Malignant tumours	Benign Lesions
1. Hormonally active tumours	
— adrenocortical carcinoma#	— adenoma secreting#:
— malignant pheochromocytoma	cortisol#
	aldosterone or
	androgens
	— pheochromocytoma#
	— micro- and macronodular adrenal hyperplasia*
	— congenital adrenal hyperplasia*
2. Hormonally inactive tumours	
— adrenocortical carcinoma	— non-secretory adenomas#
— adrenal metastases*, #	— other benign tumours (e.g. myelolipoma, angioma)
— lymphoma	— inflammatory tumours (e.g. tuberculoma)*
	— granulomas (e.g. sarcoidosis)*
	— other (e.g. cysts, haematoma)

*Frequently bilateral; #the most common causes of tumours

2. Adrenal CT — examination with contrast medium administration (washout assessment)

— In numerous health centres it constitutes a first-line examination in adrenal tumour diagnosis. It is also performed when the unenhanced CT is ambiguous in terms of the tumour nature (adenoma or "non-adenoma"), primary localisation (e.g. liver hilar tumour, pancreatic tumours), and infiltration of the surrounding tissues.

— Adrenal CT with radiation attenuation evaluation is performed prior to contrast medium administration, in the first minute (enhancement assessment), as well as in the 10th or 15th minute after contrast administration (washout assessment).

— In comparison to unenhanced CT, on the basis of this examination it is possible to assess the absolute and relative washout values (Table II) features of the surrounding tissues infiltration, as well as the presence of liver metastases.

— Basic interpretation: adenomas are characterised by faster washout – the attenuation coefficient returns quickly to basic values:
  • after 10 minutes, the absolute washout ≥ 50% (sensitivity 71–100%, specificity 80–98%), relative washout ≥ 40% (sensitivity 77–98%, specificity 94–100%);
  • after 15 minutes, the absolute washout ≥ 60% (sensitivity 86–88%, specificity 92–96%), relative washout ≥ 40% (sensitivity 96%, specificity 100%).

The method allows us to distinguish lipid-poor adenomas from other adrenal tumours in some of cases. In the case of malignant tumours (ACC, metastases), the attenuation coefficient remains elevated. However, pheochromocytoma may present various washout characteristics. Haematomas and cysts show a characteristic lack of density increase after contrast medium administration.

Table II. *Absolute and relative contrast medium washout in adrenal tumour CT*

Parameter	Formula
Absolute contrast medium washout (more frequent)	$\frac{D1'-(D10' \text{ or } D15') \times 100}{D1'-D0}$
Relative contrast medium washout	$\frac{D1'-(D10' \text{ or } D15') \times 100}{D1'}$

D0 — density (HU) prior to contrast medium administration; D1′ — density (HU) 1 minute after contrast medium administration; D10′ — density (HU) 10 minutes after contrast medium administration; D15′ — density (HU) 15 minutes after contrast medium administration

3. Adrenal MRI (most frequently without contrast medium)

— It is performed when unenhanced adrenal CT is ambiguous in terms of the tumour character. Additionally, this examination is recommended if iodine-containing contrast medium administration is contraindicated (allergies to iodine contrast mediums, renal failure, hyperthyroidism). What is more, MRI without contrast medium is the method of choice in adrenal tumours during pregnancy. In fact, adrenal MRI is characterised by high sensitivity in the diagnosis of lipid-poor adenomas (90%).

— Adrenal tumour MRI differentiation is based on chemical shift, where it is possible to obtain in-

phase and out-of-phase images. They allow for the assessment of lipid content in the adrenal tumours with higher sensitivity than unenhanced CT. In out-of-phase images a decrease in signal intensity is observed (as compared to in-phase pictures) in the lipid containing lesions (adenoma, hyperplasia), thus making the lesions hypointense. However, signal intensity in tumours not containing lipids does not change (metastases, phaeochromocytomas, ACC).

— Basic interpretation: adenoma and adrenocortical hyperplasia are characterised by a significant decrease of signal intensity in the out-of-phase. In fact, in the majority of cases, visual assessment (qualitative) allows us to distinguish lipid-containing tumours from other lesions. The signal Intensity index (SI index) calculated according to the formula: [(SI in phase–SI in out-of-phase)/SI in phase) × 100%] is employed when the visual assessment of the signal intensity decrease is ambiguous; values above 16% indicate adenoma. Pheochromocytoma present increased signal intensity in comparison to the liver and spleen in T_2-weighted images; however, it is true only in 70% of cases. Similar images are observed also in some adrenal metastases. In fact, myelolipomas are easy to diagnose in MRI (in fat-saturation sequences) due to the presence of the adipose tissue, but it frequently does not show a signal decrease in out-of-phase images.

Complementary imaging tests include:

— abdominal cavity ultrasound — the main indication is the lesion size monitoring in cases where the lesion is visible in the US image [13];
— ^{123}I-MIBG scintigraphy (or ^{131}I-MIBG scintigraphy, metaiodobenzylguanidine scintigraphy) performed in the diagnosis of pheochromocytoma;
— Positron Emission Tomography (PET) using F-fluorodeoxyglucose (FDG) — increased uptake suggests malignant tumours (ACC, metastases). False negative results may be however obtained in renal cell cancer metastases or low-grande lymphoma;
— Iodine cholesterol scintigraphy — the major indication is ACTH-independent hypercortisolism in patients with bilateral adrenal tumours qualified for surgery (please refer also to "Examinations for primary hyperaldosteronism").

4. Adrenal biopsy

Indications for adrenal biopsy are very limited. In fact, this examination may be considered in selected patients with suspected adrenal metastases of an unknown primary localisation, lymphoma, or adrenal tuberculosis if the diagnosis would change the course of treatment. A suspected pheochromocytoma or ACC constitute contraindication for biopsy.

Basic interpretation of imaging examination results is shown in Table III. It is vital to bear in mind that in spite of the huge progress in imaging examinations, in a number of cases the diagnosis of "non-adenomatous" lesions is possible only after surgery, in the course of histopathological tests [14, 15].

III. Which hormonal tests should be performed in patients with adrenal incidentaloma?

Irrespective of the clinical picture or concomitant diseases, all patients with adrenal incidentaloma should be assessed in terms of pheochromocytoma, as well as hypercortisolism [7, 9, 17–19]. Tests towards hyperaldosteronism are indicated in patients with hypertension or hypokalaemia [7, 9, 18]. Hormonal testing is usually not necessary in cases of a myelolipoma.

1. Tests for hypercortisolism

Although incidentaloma is a lesion found incidentally, it is vital to draw attention to the clinical manifestations that may accompany increased glucocorticoid secretion. Cushing's syndrome confirmation requires the presentation of increased, autonomic cortisol secretion in two tests assessing the function of adrenocorticotropic axis. Basic screening tests in the diagnosis of hypercortisolism comprise:

— Overnight dexamethasone suppression test (fasting cortisol serum concentration assessment, between 8–9 a.m. after oral 1 mg dexamethasone administration at 11 p.m. the previous day). Basic interpretation: cortisol concentration below 1.8 μg/dL (50 nmol/L) excludes hypercortisolism (sensitivity > 95%, specificity 80%). On the other hand, a cortisol concentration higher than 5 μg/dL (140 nmol/L) indicates Cushing's syndrome (sensitivity 80%, specificity 95%). Thus, in incidentaloma diagnosis, an intermediate cutoff point is employed equal to 3.4 μg/dL (94 nmol/L), characterised by 97% sensitivity and 88% specificity in the diagnosis of Cushing's syndrome (refer to subclinical hypercortisolism). Moreover, in interpretation of dexamethasone suppression test, it is possible to obtain both false positive results, in the course of depression, alcoholism, anorexia nervosa, stress, renal failure, the administration of oestrogen, tamoxifen, carbamazepine, phenobarbital, phenytoin, pioglitazone, and rifampicin, as well as false negative results, in nephrotic syndrome, administration of itraconazole, diltiazem, and fluoxetine [18, 20].
— Urinary free cortisol — increased excretion of free cortisol in 24-hour urine collection 1.5 times above

Table III. *Characteristic features of adrenal tumours in imaging examinations*

	Adenoma	Cancer	Pheochromocytoma	Metastasis
Size	Usually < 4 cm	Usually > 4 cm	No rule	No rule
Shape	Round/circular	Irregular	Round/circular	Irregular or Round/circular
Separation from the surrounding tissue	Sharp	Blurred or sharp	Sharp	Blurred or sharp
Structure	Homogenous	Inhomogeneous (necrotic areas, calcifications)	Inhomogeneous in larger tumours	Homogenous (small tumours) or inhomogeneous (larger tumours)
Unenhanced CT density	≤ 10 HU	> 10 HU (usually > 30)	> 10 HU (usually > 30)	> 10 HU (usually > 30)
Contrast washout*	≥ 50% in 10th minute	< 50% in 10th minute	Usually < 50% in 10th minute	< 50% in 10th minute
Lipid content in MRI	Definite	Lack or scant	Lack	Lack
Growth of the tumour	Stable or slow (< 0.5 cm/year)	fast (> 2 cm/year) or very fast	Frequently slow (0.5–1 cm/year)	No rule, usually fast

*Absolute contrast medium washout; on the basis of [16]

the upper limit established for a given laboratory indicates Cushing's syndrome [17].

— Late-night cortisol serum concentration (11 p.m. or 12 p.m.) above 5.4 μg/dL (140 nmol/L) indicates Cushing's syndrome (sensitivity 97%, specificity 88%). However, the disadvantage of this method is the necessity of patient hospitalisation. Late-night salivary cortisol tests are also available in Poland. However, depending on the method, reference values must be established in given laboratories.

If the screening test results are abnormal, further diagnosis in the referral centres is necessary in order to confirm the diagnosis and establish the aetiology of hypercortisolism (ACTH-dependent or ACTH-independent Cushing's syndrome).

The diagnosis of ACTH-independent, subclinical hypercortisolism remains controversial because the diagnostic criteria have not been clearly established [21]. If subclinical hypercortisolism is suspected, it is vital to consider the clinical picture (e.g. osteoporosis, visceral obesity, hypertension, diabetes) as well as the following results of additional tests (frequently 2–3 or 3–4 criteria are provided):

— 1 mg dexamethasone suppression test ≥ 3.4 μg/dL;
— morning ACTH < 5 pg/mL;
— urinary free cortisol above the upper limit;
— cortisol 11:00 p.m.–12:00 p.m. ≥ 5.4 μg/dL;
— other described criteria are as follows: decreased dehydroepiandrosterone sulphate (DHEA-S) concentration, lack of ACTH stimulation following CRH administration, the development of postoperative adrenocortical insufficiency, postoperative improvement in clinical manifestations, autonomic glucocorticoid secretion in iodocholesterol scintigraphy.

2. Tests for pheochromocytoma

Patients with incidentally found pheochromocytoma in most cases (57%) either do not present with hypertension or it is mild or moderate in character. Moreover, patients usually do not show excessive stimulation of the adrenergic system. Thus the symptom triad: diaphoresis, headache, and palpitations was present in 10% of patients diagnosed with pheochromocytoma [4].

Recommended screening tests in the diagnosis of pheochromocytoma are:

— urinary fractionated metanephrines (sensitivity and specificity depends on the method employed, although the golden standard is high-performance liquid chromatography [HPLC] where sensitivity is 95% and specificity 86%) or
— plasma free metanephrines concentration (with the use of HPLC, sensitivity 96%, specificity 89%) [7, 22–24].

Unfortunately, in Poland the abovementioned tests are available in few referral centres. Although measuring of urine unfractionated metanephrines constitutes one of the most frequently performed tests in Poland, it is no longer recommended in the diagnosis of pheochromocytoma. Nevertheless, the low price and high sensitivity stemming from careful labelling makes this test useful especially in cases of symptomatic pheochromocytoma or those larger than 2 cm [25].

Another valuable test may be assessing serum or plasma chromogranin A concentrations (sensitivity > 85%, specificity > 90%) [26–28], although there is the possibility of obtaining false positive results in the following cases: if the patient was treated with proton pump inhibitors or H_2 receptor blockers, has concomitant neuroendocrine tumours (such as carci-

Table IV. *Medications that can affect the ARR and the recommended time of their discontinuation prior to the test [7, 18, 29]*

Medication group	Influence on			Discontinuation time prior to the tests
	PRA	Aldo	ARR	
ACEI/ATRI	↑↑	↓	↓	2 weeks
Progestogens	↑↑	↑	↓	4 weeks
Diuretics/spironolactone/eplerenone	↑↑	↑	↓	4 weeks

PRA — plasma renin activity; Aldo — aldosterone; ARR — aldosterone/plasma renin activity ratio; ACEI — angiotensin-converting-enzyme inhibitors; ATRI — angiotensin receptor inhibitors

noid, gastrinoma, or glucagonoma), prostate cancer, with high levels of IgM rheumatoid factors, or some inflammatory diseases of the gastrointestinal tract (type A atrophic gastritis).

If pheochromocytoma is suspected on the basis of the clinical picture, imaging, or laboratory tests, the patient should be referred to a specialised centre. Moreover, in patients diagnosed with pheochromocytoma, it is vital to test for genetic mutations that have been demonstrated to be related with the development of pheochromocytoma.

3. Tests for primary hyperaldosteronism

The screening test for primary hyperaldosteronism is aldosterone-renin ratio (ARR) based on the ratio of aldosterone (ng/dL) and plasma renin activity (ng/mL/h) or renin concentration measured in the morning, two hours after upright standing, taken while sitting. Basic interpretation: in order to diagnose primary hyperaldosteronism ARR should be > 30, and aldosterone concentration should be above 10–15 ng/dL [29, 30]. When interpreting ARR it is necessary to take into consideration the influence of any taken medications (Table IV). Prior to the planned diagnostic procedures, potassium deficiency should be supplemented and if possible hypertension medications should be modified because long-lasting calcium channel blockers and α_1-adrenolytics may minimally influence the ARR value. Additionally, a diet without sodium restrictions is recommended.

Patients with abnormal results of the abovementioned markers require further diagnosis in referral centres. Should primary hyperaldosteronism be confirmed in patients qualified for surgical treatment, it is necessary to consider catheterisation of adrenal veins in order to assess the lateralisation of aldosterone secretion, independently of the adrenal tumour presence. Adrenal iodocholesterol scintigraphy is rarely employed.

4. Tests for hyperandrogenism

In females with hyperandrogenic syndrome, total testosterone measurement is recommended along with dehydroepiandrosterone sulphate (DHEA-S) and 17(OH)-progesterone levels. High concentrations of testosterone (over 200 ng/dL), DHEA-S (over 800 μg/dL), and 17(OH)-progesterone frequently accompany ACC [11, 31]. Abnormalities in androgen levels require differentiation with polycystic ovarian syndrome and congenital adrenal hyperplasia [32, 33].

IV. What are the indications for the surgical treatment of an incidentaloma?

Surgical treatment constitutes a crucial integral component in managing patients with adrenal incidentaloma. Surgical treatment should be offered to patients with adrenal incidentaloma where imaging examinations suggest a malignant lesion (oncological recommendation) or with confirmed hormonal activity (endocrinological recommendations).

1. Oncological recommendations

The most important criterion is a radiological tumour image that does not correspond to an adrenal adenoma (density in unenhanced CT over 30 HU, contrast medium washout <50% in the 10th minute or lack of lipids in MRI) (Table III).

Additional criteria include:

— Tumour size (diameter > 5 cm);
— Fast or very fast tumour growth (Table III).

Indications for the surgical removal of adrenal metastases should be approached individually if the primary tumour has been removed and no metastases have been confirmed.

2. Endocrinological indications:

— All cases of a suspected pheochromocytoma because even asymptomatic tumours may be the cause of the hypertension crisis, e.g. during other surgical procedures.
— ACTH — independent Cushing's syndrome. Due to the increased mortality of Cushing's syndrome patients, tumours overproducing cortisol should be removed. Surgical treatment recommendations may be difficult in bilateral adrenal tumours (indication for iodocholesterol scintigraphy). Surgical treatment of subclinical hypercortisolism patients is

controversial. In fact, surgical intervention should be considered especially in younger patients suffering from diseases associated with cortisol excess (e.g. recent confirmation or deterioration of hypertension pharmacological control, type 2 diabetes, or osteoporosis) [21, 34, 35].
— Primary hyperaldosteronism. In primary hyperaldosteronism patients in the course of adrenal adenoma (Conn's syndrome) it is vital to consider surgical treatment first.
— Hyperandrogenic syndrome associated with adrenal tumour.

3. Types of surgery

The choice of the surgical method should be based primarily on the surgical team's experience and skills. Additional factors influencing the decision comprise: tumour size, surgical treatment indications, concomitant diseases, risk factors, anatomical conditions, the patients' physique, and the team's technical capabilities.

The invention of minimally invasive adrenal surgery methods in the late 20th century changed modern surgery without changing indications for surgical procedures, their rules of conduct, or their goals and scope. In fact, the safety advantages and patient satisfaction combined with a simultaneous decrease in perioperative and postoperative complications made the videoscopic/laparoscopic surgery the point of reference. The versatility of laparoscopic surgery (lateral access to the adrenals from the peritoneal cavity) has led to the fact that 85% of health centres employ it as a basic treatment method. Therefore, what should rather be discussed are not indications for this method, but cases where classical open surgery is advisable [36–38].

Adrenalectomy indications for classical open surgery:
— Patients with larger adrenal tumours (> 8 cm);
— ACC patients with invasive tumour features, such as local infiltration, lymph node enlargement, metastases to distant organs;
— Patients requiring adrenal reoperation.

Non-radical, adrenal sparing adrenalectomies are rarely performed. The aim of such operations is the removal of the lesion responsible for surgery indications (tumour) with the retention of a well-vascularised unchanged portion of the adrenal cortex. Thus, it allows adrenal function to be maintained and, as a consequence, to avoid substitutional treatment [37, 39]. However, the indications for non-radical adrenal sparing adrenalectomy remain unclear. This kind of surgery may be considered in patients:
— qualified for bilateral adrenalectomy;
— with hereditary multiple endocrine neoplasia comprising pheochromocytoma;
— with a pseudocyst or an endothelial adrenal cyst.

V. Preparations for surgery and postoperative care

1. Incidentally found pheochromocytoma

The following aspects play a crucial role in patient preparation for surgery [24, 40–43]:
— proper filling of vascular bed;
— blood pressure normalisation, including controlling paroxysmal hypertension and symptoms depending on the circulating catecholamine excess which may be released during the surgery itself;
— heart rate normalisation.

The preparation period usually lasts 2–3 weeks when alpha receptor blockers are administered:
— Doxazosin in a gradually increasing dose: from 1 mg to 12–16 mg daily, in the days prior to the surgery, usually divided into three doses,
— Phenoxybezamine — 20–100 mg daily administered orally in 2–3 divided doses.

Calcium antagonists (dihydropyridine derivatives) may be used in connection with alpha blockers as a means of preparation for surgery. In patients with tachycardia or with concomitant arrhythmias, introducing selective beta-adrenolytics should be considered only after **alpha receptor blockage**. Hypovolaemia should be treated using increased salt and fluid oral intake, as well as intravenous 0.9% sodium chloride infusions before surgery and during its course. Sudden blood pressure rise during surgery should be controlled by administration of: IV phentolamine 2-5 mg (repeating the dosage if necessary), sodium nitroprusside, or urapidil. **Nevertheless, hypotension is the greatest potential danger in post-op patients.** Sudden catecholamine decrease leads to vascular bed dilation and reduced cardiac output. What is more, if combined with decreased blood volume and blood loss in the course of surgery, it may result in sudden blood pressure drops.

The following patient condition features are considered proper before the surgery:
— if in the 24-hour period immediately before the surgery no significant high blood pressure episodes > 160/90 mm Hg appear, as well as no episodes of orthostatic hypotension < 80/45 mm Hg are noted;
— if there is neither tachycardia at rest nor any significant arrhythmia;
— if there is no ST segment elevation and T-wave inversion in the ECG in the seven-day period prior to operation.

Due to the lack of clear histopathological diagnosis of pheochromocytoma, patients require lifelong ambulatory care.

2. Incidentally found primary hyperaldosteronism

Preparation for surgery requires potassium supplementation [9, 30, 44–46]. This process is achieved by a diet

that is low in sodium and rich in potassium, as well as by spironolactone administration 100–400 mg daily for a few weeks before the procedure. Blood pressure normalisation and normokalaemia are considered necessary conditions in order to perform surgery.

After surgery potassium supplements and spironolactone should be discontinued, and hypertension drugs should be gradually reduced. Moreover, hyperkalaemia may appear as a consequence of decreased aldosterone secretion by the adrenal gland. Usually, a sodium-rich diet is sufficient, although rarely patients also require the temporary administration of fludrocortisone. Hence, effective surgical treatment is based on the normalisation of aldosterone concentrations and plasma renin activity.

In the case of idiopathic bilateral adrenocortical hyperplasia, the method of choice is pharmacological treatment based on spirolactone administration, firstly 100–200 mg daily. In order to continue the treatment, smaller doses of 50–100 mg daily are usually required. Another recommended medication is eplerenone (competitive aldosterone antagonist), which may be considered in the case of adrenocortical hyperplasia.

3. Subclinical hypercortisolism

In the case of subclinical hypercortisolism steroidogenesis inhibitors are not employed. Patients with subclinical overproduction of glucocorticoids always require steroid cover during and after the surgery. The patient should be administered 100–200 mg of hydrocortisone intravenously at the day of surgery, with gradually reduced dosage in the consecutive days until oral administration. Postoperative adrenocortical insufficiency is the most conclusive confirmation of subclinical hypercortisolism. After successful surgical treatment the adrenal function normalises within 6–24 months. In fact, permanent adrenocortical insufficiency after unilateral surgical procedure is extremely rare [7, 9, 21, 36].

4. Adrenocortical cancer (ACC)

In patients with suspected ACC, the surgical procedure should be performed with steroid cover if hormonally active adrenal tumours were found in the preoperative period. After surgery, mitotane administration should be considered [5, 6, 31].

5. Adrenocortical insufficiency

Bilateral adrenal tumours, such as metastases, lymphoma, and tuberculosis, may cause adrenal insufficiency, if 90% of the adrenal cortex has been destroyed. In fact, the most common cause are metastatic lesions in the adrenals. In this group of patients — if they are qualified for surgical removal of the abnormal adrenal gland — the surgical procedure should be performed with steroid cover.

6. Hormonally inactive adrenal tumours

The majority of diagnosed adrenal tumours do not show any clinical or subclinical hormonal activity, and thus they do not require any preparation for surgery. Postoperative treatment depends on histopathological diagnosis and adrenal function assessment after surgery, which, apart from the interview and physical examination, includes cortisol and ACTH concentration assessment, as well as the electrolyte serum concentration estimation in the morning. The percentage of patients who develop postoperative adrenocortical insufficiency or a decrease in adrenal reserve after unilateral adrenalectomy is small [41].

VI. What are the problems with histopathological adrenal tumour assessment?

Despite great progress in histopathological techniques, such as immunohistochemistry, morphological diagnosis of resected abnormal adrenal masses still remains a challenge and may lead to mistakes, e.g. the percentage of initial incorrect histopathological diagnoses in Germany was estimated at 13% [5]. However, neoplasms, both primary and metastatic, constitute the majority of resected adrenal lesions (Table V).

The challenges pathomorphologists face during diagnosis are directly related to the four basic issues they strive to establish:

1. Is it a neoplasm or is it a non-neoplastic lesion?
2. Is the tumour primary or secondary in nature (adrenal metastasis)?
3. Does the tumour originate in the cortex or the adrenal medulla?
4. Is the neoplasm benign (e.g. adrenal adenoma) or it is malignant (e.g. adrenocortical carcinoma)?

Ad 1. A large portion of adrenal lesions are non-neoplastic tumours, for example: inflammatory lesions (mainly tuberculous), nodular adrenocortical hyperplasia, or adrenal cysts (both pseudocysts and epithelial-lined/true cysts). However, they are relatively rarely treated surgically and thus constitute a minority of postoperative morphological diagnoses. [48, 49].

Ad 2. Adrenals are relatively common sites of metastatic tumours. They are the fourth most frequent location of metastases (after the lungs, liver, and bones). According to the literature, metastases to the adrenals are present in 27% of patients dying due to carcinomas. Most often, these metastases are from lung, breast, kidney, and gastrointestinal tract carcinomas, as well as from malignant melanomas. In certain cases, differentiation of metastases with primary tumours, usually cortical, may constitute a problem; this applies mainly to tumours with clear cytoplasm, such as clear

Table V. *WHO classification of adrenal tumours [47]*

PRIMARY ADRENAL TUMOURS	
Adrenal cortical tumours	
Adrenal cortical carcinoma	8370/3
Adrenal cortical adenoma	8370/0
Adrenal medullary tumours	
Malignant pheochromocytoma	8700/3
Benign pheochromocytoma	8700/0
Composite Pheochromocytoma/Paraganglioma	
Other adrenal tumours	
Adenomatoid tumour	9054/0
Sex-cord stromal tumor	8590/1
Myelolipoma	8870/0
Teratoma	9080/1
Schwannoma	9560/0
Ganglioneuroma	9490/0
Angiosarcoma	9120/3
SECONDARY TUMORS	

cell renal cell carcinoma (CCRCC), or tumours with a trabecular growth pattern, such as hepatocellular carcinoma (HCC). In such cases, the immunohistochemical markers of cortical differentiation play a major role. Among the numerous markers used in the course of primary adrenocortical tumour identification, the most practical (with relatively high sensitivity and specificity) are steroidogenic transcription factor-1 (Ad4BP/SF-1), melanoma-A marker (MART-1), and inhibin-alpha. However, one has to bear in mind that in some percentage of extra-adrenal tumours, the above-mentioned markers may give a false positive result, e.g. RCC presents a positive reaction with melan-A in 10% of cases and in 9% of cases with inhibin-alpha [50]. It is helpful to use immunohistochemical markers that are typically positive for the primary malignancy, e.g. Hep-Par-1 positive reaction in HCC, PAX8 positive in RCC, or TTF-1 positive in the large portion of lung carcinomas. The majority of metastatic tumours retain both the primary tumour morphology and immunophenotype, thus the immunohistochemical panel does not differ from the diagnostic standards for primary lesions. It is vital to stress the importance of clinical data, such as detailed information regarding past neoplastic diseases, in the planning of a morphological differential diagnosis concerning the primary and secondary adrenal tumours.

Ad 3. In routine histopathological haematoxylin and eosin staining (H&E), differentiation between pheochromocytoma and adrenocortical tumour (especially ACC) may pose certain difficulties. Hence, it may be very helpful to use immunohistochemistry. Chromogranin A is most often used in the differentiation of cortical and medullary tumours because it is almost always negative in cortical tumours and remains positive in 100% of pheochromocytoma cases. Other neuroendocrine markers, such as synaptophysin or NSE, are less frequently employed. In fact, although they nearly always exhibit a positive reaction in medullary tumours, they also remain positive in a large group of cortical tumours, e.g. synaptophysin exhibits a positive reaction in 67% of cortical tumours. Typical markers for adrenocortical tumours may show positivity in a small group of phaeochromocytomas, e.g. α-inhibin and melan-A in 6% of cases and calretinin in 14% of phaeochromocytomas [51]

Ad 4. The most crucial issue in adrenal tumour morphological analysis is the assessment of the lesion's malignancy potential, especially in adrenocortical tumours. Apart from local invasion and distant metastases, there are hardly any isolated, single morphological features of malignancy. Nevertheless, basic macroscopic features are useful in the initial differential diagnosis. Adrenocortical adenomas usually weigh below 50 g, they are well-circumscribed, non-encapsulated, or encapsulated lesions (with a true or pseudocapsule). Macroscopically, they usually have a homogenous, solid, and uniform structure, most frequently yellowish or yellowish-orange colour. ACCs, on the other hand, are typically large lesions weighing over 100 g and measuring more than 6 cm. Grossly, they are heterogenous tumours, varied in colour (from yellowish-orange to brown), of lobulated structure with fibrous bands, frequently with areas of necrosis and haemorrhage. ACCs may be well-demarcated, but they frequently infiltrate the surrounding tissues and adjacent organs, e.g. the kidney or liver.

Nevertheless, numerous microscopic parameters play a major role in the assessment of adrenocortical tumour malignant potential. To date, few multi-parametric systems assessing the primary adrenocortical tumour histologically for malignant potential have been developed. Some of them are based only on morphological features, others also include clinical and biochemical criteria. The most commonly used and the most verified criteria for assessing malignant potential in adrenocortical tumours is the Weiss system, which is also recommended by the Polish Society of Pathologists [49]. It is based on the assessment of nine histological features, each equal to one point in the scoring system. It is not a perfect system, its greatest disadvantage being poor reproducibility and subjectivity in the assessment of certain parameters. Therefore, Aubert et al. suggested its modification with the exclusion of the most controversial features (Table VI). Tumours scoring three or more points in each system correlate with malignancy and are diagnosed as ACCs [53].

Table VI. *Histological criteria for assessment of malignant potential in adrenocortical tumours [53]*

	Weiss System	Modified Weiss system
High nuclear grade (grade 3 or 4 based on Fuhrman criteria)	√	–
Mitotic rate greater than 5 per 50 high-power fields	√	√ × 2
Atypical mitoses	√	√
Clear cells comprising 25% or less of the of tumour	√	√ × 2
Diffuse architecture in over 1/3 of tumour	√	–
Necrosis	√	√
Venous invasion (smooth muscle in wall)	√	–
Sinusoidal invasion (no smooth muscle in wall)	√	–
Capsular invasion	√	√

Another frequently employed system of measuring the adrenocortical tumour malignancy potential is the van Slooten system, which analyses seven histological features attributing a numerical score (1.6–9.0). A total value of the features, also known as the van Slooten Index (VSI), ≥ 8 correlates with malignant behaviour [54].

It is worth bearing in mind that, due to the morphological and clinical distinctiveness of adrenocortical tumours in children (usually less aggressive clinical course with a similar histopathological picture), the abovementioned systems may be employed only in adult patients (over 20 years of age). What is more, using Weiss system criteria, as well as the modified Weiss system, may also be problematic in cases of one adrenocortical tumour subtype, i.e. oncocytic adrenocortical tumour [51, 53–56].

Similarly to adrenocortical tumours, the assessment of pheochromocytoma malignancy also constitutes a challenge for the histopathological diagnosis. On the basis of the updated WHO classification of tumours, malignant pheochromocytoma is defined exclusively on the basis of the presence of metastases at sites where paraganglial tissue is not normally found. A significant challenge in the morphological diagnosis of pheochromocytoma is the assessment of the tumour's malignant potential before metastases occur. Moreover, there are no clearly defined criteria concerning differentiation between benign and malignant pheochromocytoma. The most frequent microscopic features in malignant tumours are: nodular structure, confluent necrosis, absence of hyaline globules, high mitotic index, atypical mitotic figures, absence of sustentacular cells (identified by immunohistochemical staining with S100 protein), as well as Ki-67 (MIB-1) proliferative index above 2.5%. Similarly to adrenocortical tumours, in the diagnosis of pheochromocytoma, scoring systems are employed based on a number of morphological features [53]. Thompson's system, also known as Pheochromocytoma of the Adrenal Gland Scoring Scale (PASS score), is most frequently used. It is based on the analysis of numerous morphological features where 1–2 points are attributed. Two-point features include: the tumour's structure with large nests or diffuse growth, the presence of necrosis, high cellularity, cellular monotony, presence of spindle shaped tumour cells, more than three mitoses for 10 high-power fields, atypical mitoses, and extension of the tumour into adjacent fatty tissue. One-point features include: invasion of tumour cells into vessels, infiltration of the capsule, nuclear pleomorphism, as well as nuclear hyperchromasia. Each tumour may receive as many as 20 points. Benign phaeochromocytomas have fewer than four points in the PASS system, malignant ones have more than six points, although patients scoring more than four points should followed-up due to the risk of tumour recurrence. A critical approach to this system is recommended. Apart from Thomason's system, which is based on histological features, other suggestions regarding pheochromocytoma differentiation are presented in the literature. The most vital one is Kimura's scoring system, which is based not only on assessment of the histological features but also on the Ki-67 proliferative index and the type of catecholamines secreted by the tumour [54]. However, it is worth remembering that there is no golden histopathological standard that would be accepted by everyone when it comes to differentiating between benign and malignant phaeochromocytomas.

VII. How to monitor adrenal tumours not qualified for surgical treatment

There is no clear agreement regarding monitoring of adrenal incidentalomas that are not qualified for surgical treatment. Control tests (both imaging and laboratory) should be planned individually taking into consideration such factors as tumour size, image and growth dynamics, clinical manifestations, hormonal tests results, as well as concomitant diseases, including neoplasms [57–63].

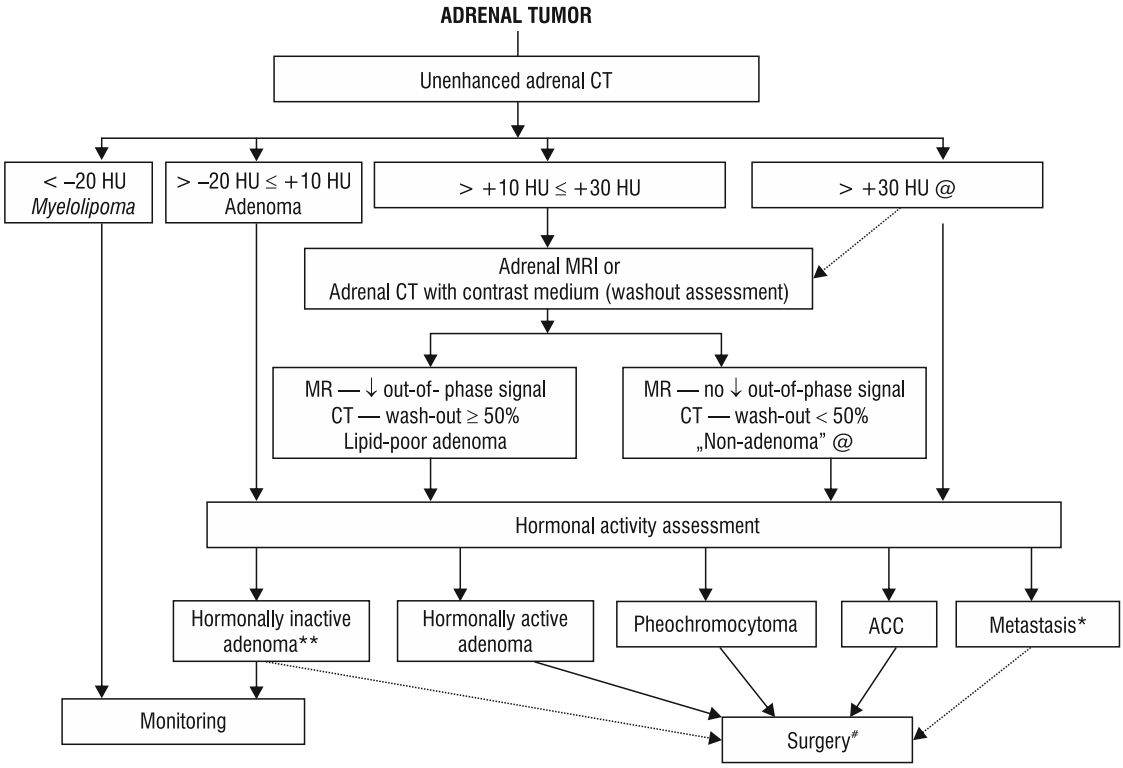

Figure 1. *Management of adrenal incidentaloma. In numerous centres adrenal CT with contrast medium (washout assessment) is the first line examination in the diagnosis of adrenal tumours; @ — individual approach to focal lesions — the clinical picture should be considered, as well as concomitant diseases, tumour size, and growth dynamics. Indications for other tests, e.g. scintigraphy, PET-CT, and adrenal biopsy, should be taken into account; *search for primary localisation. Surgical removal of adrenal metastasis may be considered in isolated metastasis and primary localisation removal; **indications for surgery in patients with hormonally inactive adenomas should be approached individually, taking into consideration lesion size, growth dynamics, the patient's age, and concomitant diseases; #hormonally active adrenal tumours (especially phaeochromocytomas) require pharmacological treatment prior to surgery; CT — computed tomography; MRI — magnetic resonance imaging; HU — hounsfield units*

1. Imaging tests

— Basic tests monitoring tumour size comprise: US of the abdominal cavity and unenhanced adrenal CT. US constitutes an inexpensive and reliable method monitoring adrenal tumours, especially those larger than 3 cm in diameter localised in the right adrenal gland.
— When the tumour is ≤ 3 cm in diameter and resembles a typical lipid-rich adenoma, imaging tests are recommended every 12 months. In the cases of larger tumours, or those with a less characteristic phenotype, it is worth considering check-ups every 3–6 months within the first year, and later every 12 months.
— If the adrenal lesion is not oncologically suspicious and is stable, monitoring may be ceased after four years. In further observation, the risk of malignant transformation is practically non-existent.

2. Hormonal tests

— In adrenal tumours which are not hormonally active "based on" on clinical examination, monitoring includes only a selective hormonal assessment every 12 months. A screening with 1 mg dexamethasone suppression test is recommended; screening tests for pheochromocytoma may be considered. Tumours larger than 3 cm are more frequently hormonally active than smaller lesions [61]. The risk of an excessive hormonal secretion by an adrenal tumour reaches a plateau after 3–5 years [58]; hence, further control is not necessary.
— Patients with suspected subclinical hypercortisolism require control tests assessing adrenocortical axis function as well as a precise control of the diseases associated with an excess of glucocorticoids (obesity, diabetes, hypertension, osteoporosis).
— The risk of developing pheochromocytoma in an initially unsuspicious adrenal tumour is very low. Unfortunately, the CT picture in the aforementioned cases may suggest lipid-poor adrenocortical adenomas. Thus, in such a case hormonal tests may be key for the diagnosis.

VIII. Conclusions

A simplified algorithm for the diagnostic management is shown in Figure 1.

— Adrenal incidentaloma is an abnormal lesion ≥ 1 cm in diameter, found incidentally during imaging examination. Every focal lesion in adrenals found in US requires confirmation by CT or MRI.
— The main goal of imaging tests is the differentiation between adenomas and "non-adenomas" requiring further diagnosis for ACC, adrenal metastasis or pheochromocytoma. Basic imaging tests include: unenhanced adrenal CT, adrenal CT with contrast medium (washout assessment), and adrenal MRI (most frequently without contrast medium).
— In all adrenal incidentaloma patients, notwithstanding the clinical picture and concomitant diseases, tests for pheochromocytoma and hypercortisolism are recommended. Tests for primary hyperaldosteronism are indicated in patients with diagnosed hypertension and hypokalaemia.
— Adrenal incidentalomas with malignancy features in the imaging test (oncological recommendations), as well as those with diagnosed hormonal activity (endocrinology recommendations), require surgical treatment. The principal surgical procedure is videoscopic/laparoscopic adrenalectomy. Hormonally active adrenal tumours (especially suspected pheochromocytoma) require pharmacological treatment prior to surgery.
— Control tests (imaging and laboratory) in patients not qualified for surgical treatment should be planned individually taking into considerations such features as: tumour size and growth dynamics, clinical manifestations, hormonal test results, and concomitant diseases.

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